CONCEPT PAPER

RISK ASSESSMENT OF OBSERVATIONAL DATA: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT

DRAFT

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If you plan to submit comments on this concept paper, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include an alternative proposal and the rationale and/or justification for employing the alternative.*
- *Identify specific comments by line numbers; use the pdf version of the document whenever possible.*

I. INTRODUCTION

In accordance with Section VIII of the PDUFA III Reauthorization Performance Goals and Procedures, the CDER/CBER Pharmacovigilance Working Group is drafting guidance for industry on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drug and biological products.[1] This concept paper is intended to facilitate public discussion on the content of the draft guidance by outlining FDA's proposed approach and requesting comment. Specifically, this concept paper presents FDA's preliminary thoughts on:

- Important pharmacovigilance concepts
- Safety signal identification
- Pharmacoepidemiologic assessment and interpretation of safety signals
- The development of pharmacovigilance plans

II. IMPORTANT PHARMACOVIGILANCE CONCEPTS

A. What is pharmacovigilance?

Pharmacovigilance is generally regarded as all postapproval scientific and data gathering activities relating to the detection, assessment, understanding, and prevention of adverse events or any other product-related problems. This includes the use of pharmacoepidemiologic studies.

While the product development process is very rigorous, it is not possible to detect all safety concerns during clinical trials. As a result, postapproval safety data collection and risk assessment based on observational data are critical to evaluating and minimizing a product's risk profile. Once a product is marketed, there is generally a large increase in

[1] For ease of reference, this concept paper uses the terms *product* and *drug* to refer to all products (excluding blood products other than plasma derivatives) regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). Similarly, for ease of reference, this concept paper uses the term *approval* to refer to both drug approval and biologic licensure.

the number of patients exposed, including those with co-morbid conditions, and those being treated with concomitant medical products. Safety signals identified from case reports may be further evaluated in pharmacoepidemiologic studies, registries or surveys. A safety signal may be described as an apparent excess of adverse events associated with a product's use. Occasionally, however, even a single well-documented case report, particularly if the report describes a positive rechallenge, may be viewed as a signal. In addition, preclinical findings with the product or experience with other similar products in the class may be sufficient to generate a safety signal even in the absence of adverse event reports in patients.

Safety signals may be further assessed in terms of their magnitude, the population(s) at risk, changes in risk over time, biologic plausibility, and other factors. A product's risk profile may be characterized by several safety signals.

B. Does this concept paper discuss all aspects of risk assessment?

No, this concept paper solely focuses on issues surrounding the assessment of a product's risk profile as identified from observational data sources (including case reports, case series, and pharmacoepidemiologic studies). Generally, ongoing assessment of a product's risk profile from observational data is performed after approval. Risk assessment based on clinical study data during product development is addressed by a separate concept paper entitled *Premarketing Risk Assessment*.

C. What is a pharmacovigilance plan?

We envision a pharmacovigilance plan as being a plan proposed by a sponsor for the ongoing evaluation of identified safety signals through enhanced pharmacovigilance practices. For example, a pharmacovigilance plan may involve (1) expedited reporting of certain serious adverse events, which would otherwise only be subject to periodic reporting, (2) implementation of active surveillance activities, and/or (3) conduct of additional observational studies or clinical trials.

D. How does a pharmacovigilance plan differ from a risk management program (RMP)?

As currently defined in a companion concept paper (*Risk Management Programs*), a risk management program (RMP) would be a submission to FDA that comprehensively analyzes a product's risk profile and proposes active interventions to minimize them. While a pharmacovigilance plan might be a component of a larger RMP, its sole focus would be to assist in detecting new signals and/or evaluating already identified safety signals.

III. HOW ARE SAFETY SIGNALS BEST IDENTIFIED FROM CASE REPORTS AND CASE SERIES?

Good pharmacovigilance practice generally starts by acquiring complete data from spontaneous adverse event reports, also known as case reports. The reports are used to develop case series for interpretation.

A. What are the characteristics of a good case report?

It is critical for sponsors to actively seek information on an adverse event by direct contact with the initial reporter so that a thorough assessment of the event can be made expeditiously. If the sponsor is unable to acquire all of the relevant information prior to the submission of its first case report, follow-up information may be submitted. The intensity and method of case follow-up would be driven by the seriousness of the event reported, its origin (e.g., healthcare provider, consumer, literature) and other factors. The most aggressive follow-up efforts would be directed towards validating serious, unexpected adverse event reports that lack details deemed important for case assessment.[2]

Although this paper will not repeat the extensive discussion of good adverse event reporting practices contained in several other guidances,[3] we emphasize that a good case report, whether reported spontaneously or published in the medical literature, describes the following:

1. Details of the adverse event(s) reported
2. Baseline patient characteristics including co-morbid conditions, use of concomitant medications, and presence of risk factors
3. Therapy details (i.e., dose, dates and/or duration)
4. Time to onset of signs or symptoms
5. Method of diagnosis of the event
6. Clinical course of the event and outcomes (e.g., hospitalization or death)
7. Laboratory studies at baseline and during therapy including drug levels, as appropriate
8. Any other relevant information

For reports of medication errors,[4] a good case report would also include a full description of the following:

1. Product(s) involved (including the proprietary and generic name, manufacturer, dosage form, strength, concentration, and type and size of container)

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[2] Current Challenges in Pharmacovigilance: Pragmatic Approaches, Report of CIOMS Working Group V, Geneva 2001.

[3] *See* (1) *Guideline for Postmarketing Reporting of Adverse Experiences*, (2) Guidance for industry: *E2C Clinical Safety Data Management: Periodic Safety Update Report (PSUR)*, (3) Guidance for industry: *Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report*, and (4) Draft Guidance to industry: *Postmarketing Safety Reporting for Human Drugs and Biologics Including Vaccines*.

[4] Please refer to http://www.nccmerp.org for the definition of a medication error and taxonomy of medication errors.

2. Sequence of events leading up to the error
3. Work environment in which the error occurred
4. Types of personnel involved with the error

We encourage sponsors to include in the case narrative all of the data elements outlined in the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) taxonomy as appropriate.

B. How are case series developed?

When reports of two or more cases are identified in adverse event databases that associate a similar event with a product, a case series could be developed. In FDA's experience, the development of a case series through the identification of additional clinically relevant cases depends on thorough database search strategies based on Medical Dictionary for Regulatory Activities (MedDRA) terminology. Generally, case definitions would be developed to provide consistent characterization of the adverse events in question and to facilitate retrieval of all clinically relevant cases from the database.[5] In addition, datamining techniques may be applied to the database to identify relevant cases. Clinical information would be summarized for the entire case series and for relevant subsets as appropriate (e.g., by demographic subgroups, by outcome).

IV. HOW ARE SAFETY SIGNALS BEST EVALUATED IN PHARMACO-EPIDEMIOLOGIC STUDIES?

When a safety signal is identified from spontaneous case reports, literature reports, or other sources, further evaluation of the signal may be possible via carefully designed pharmacoepidemiologic studies, registries, and surveys.

A. When and why are pharmacoepidemiologic studies recommended?

Pharmacoepidemiologic studies of various designs (cohort, case-control, nested case-control, or other hybrid designs) permit a sponsor to further characterize one or more safety signals associated with a product as it is used in the "real world." In particular, if a sponsor wishes to evaluate a concern that is not readily assessable in a controlled clinical trial, such as (1) chronic exposure to a product or (2) exposure in populations with co-morbid conditions or taking multiple concomitant medications, the sponsor could conduct a pharmacoepidemiologic study. The size of the study would depend on the expected frequency of the event(s) of interest. Sponsors may initiate studies at any time. Typically, they are started at the time of initial marketing based on questions that remain after review of the premarket data, or when a safety signal has been identified after approval.

[5] A case definition for acute liver failure, for example, could specify liver function test abnormalities, evidence of coagulopathy, altered mental status, need for liver transplantation or other clinical details.

There are a number of references describing methodologies for pharmacoepidemiologic studies [6,7] and providing guidelines to facilitate the conduct, interpretation and documentation of such studies.[8] Consequently, this paper will not comprehensively address these topics. However, based on FDA's experience, a pharmacoepidemiologic study protocol minimally would contain:

1. Clearly specified study objectives
2. A critical review of the literature
3. A detailed description of the research methods including
    - population to be studied
    - data sources to be used
    - projected study size
    - methods for data collection, management and analysis

In recent years, pharmacoepidemiologic studies have been conducted in automated claims databases (e.g., HMO or Medicaid) that allow retrieval of records of product exposure and patient outcomes. Depending on study objectives, factors that may impact the choice of databases selected would include the following:

1. Demographic characteristics of patients enrolled in the health plan(s) (e.g., age and geographic location)
2. Turnover rate of patients in the health plan(s)
3. Plan coverage of all medications of interest
4. Size of the exposed population available for study
5. Availability of the outcome(s) of interest
6. Ability to identify outcomes of interest using standard coding systems (e.g., International Classification of Diseases [ICD-9])
7. Access to medical records

Based on FDA's experience, validation of diagnostic findings in claims database studies through detailed review of at least a sample of medical records is essential for all pharmacoepidemiologic studies.

B. When and why would registries be established?

The term "registry" as used in pharmacovigilance and pharmacoepidemiology is often given different meanings. For the purpose of this concept paper, we are defining a registry as a systematic collection of defined events or product exposures in a defined

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[6] Strom BL (ed), 2000, *Pharmacoepidemiology*, 3rd edition, Chichester: John Wiley & Sons, Ltd.

[7] Hartzema AG, Porta M, and Tilson HH (eds), 1998, *Pharmacoepidemiology: An Introduction*, 3rd edition, Cincinnati, OH: Harvey Whitney Books.

[8] "Guidelines for Good Epidemiology Practices for Drug, Device and Vaccine Research in the United States," International Society for Pharmacoepidemiology, 1996 (http://www.pharmacoepi.org/resources/goodprac.htm).

patient population for a defined period of time.[9] Through the creation of registries, a sponsor can monitor for safety signals identified from spontaneous case reports, literature reports, or other sources, and evaluate factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or other patient characteristics.[10]

A sponsor could initiate a registry at any time. The decision to establish a registry would include consideration of the type of additional risk information desired and the feasibility of establishing the registry. It may be appropriate to initiate the registry at the time of initial marketing, when a new indication is approved, or when there is a desire to evaluate safety signals identified from spontaneous case reports.[11]

Ideally, a written protocol would provide objectives for the registry, and a review of the literature and available animal and human data. It would also contain a detailed description of the research methods including (1) patient recruitment and follow-up, (2) projected sample size, and (3) methods for data collection, management and analysis. Essential elements of a registry-based monitoring system would include carefully designed data collection forms to ensure data quality and integrity, and validation of registry findings against a sample of medical records or via interviews with health care providers.[12]

C. When and why would surveys be performed?

Patient or health care provider surveys are possible approaches for gathering information to:

1. Further evaluate safety signals
2. Assess knowledge about labeled adverse events
3. Assess use of a product as labeled, particularly when the indicated use is for a restricted population or numerous contraindications exist
4. Assess compliance with the elements of a risk management program (e.g., whether or not a Medication Guide was provided at the time of product dispensing)[13]
5. Address confusion in the practicing community over sound-alike or look-alike proprietary names

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[9] See footnote 2. Supra.

[10] Guidance for industry: *Establishing Pregnancy Exposure Registries*.

[11] Ibid.

[12] Ibid.

[13] For a detailed discussion of risk management program evaluation, please refer to the concept paper entitled *Risk Management Programs*.

As with registries, surveys can be initiated by sponsors at any time. They can be conducted at the time of initial marketing (i.e., as a postmarketing commitment) or when there is a desire to evaluate safety signals identified from spontaneous case reports.

Ideally, a written protocol would provide objectives for the survey, and a detailed description of the research methods including (1) patient or provider recruitment and follow-up, (2) projected sample size, and (3) methods for data collection, management and analysis. Essential elements of a survey-based monitoring system would include carefully designed survey instruments and validation of survey findings against a sample of medical or pharmacy records or via interviews with health care providers.

D. How are privacy and human subject protections ensured?

It is critical that protocols for pharmacoepidemiologic studies, including those for registries and surveys, provide measures to protect the confidentiality of individual patients' records. At minimum, they must comply with ethical principles and regulatory requirements involving human subjects research as specified in the Federal regulations for the protection of human subjects (45 CFR part 46 and 21 CFR parts 50 and 56). Even for those designs thought to fall in the category of surveillance as opposed to a formal study, we recommend that sponsors use informed consents and consult with an institutional review board (IRB) as appropriate.[14]

V. HOW ARE SAFETY SIGNALS BEST ASSESSED AND INTERPRETED?

Safety signals may be assessed in terms of their magnitude, population(s) at risk, changes in risk over time, biologic plausibility and other factors. Safety signals may inform us about the following:

1. New unlabeled adverse events
2. An observed increase in the severity or specificity of a labeled event
3. An observed increase in the frequency of a labeled event
4. New product-product, product-food, or product-dietary supplement interactions
5. Confusion with a product's name, labeling, packaging or use, either actual or potential

A. Calculating incidence rate and reporting rates: what is the magnitude of the safety signal?

Calculations of the rate at which new cases occur in the exposed population (i.e., the incidence rate) are the hallmark of pharmacoepidemiologic risk assessment. In pharmacoepidemiologic studies, the numerator (number of new cases) and denominator (number of exposed patients) may be readily available. For spontaneously reported events, it is not possible to identify all cases due to under-reporting, and the size of the

[14] "Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health," International Society for Pharmacoepidemiology, 1997 (http://www.pharmacoepi.org/resources/privacy.htm).

exposed population is at best an estimate. Limitations in denominator estimates arise because:

1. it may be difficult to exclude patients who are not at risk for an event because their exposure is too brief or their dose is too low[15]
2. estimates of the size of the patient subset at risk for a particular event are not available

Although we recognize these limitations, we believe that the calculation of reporting rates using spontaneously reported cases and estimates of patient exposure from prescription or patient level data may be a valuable step in the assessment of adverse events. FDA recognizes the value of comparisons of reporting rates across similar products or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial confounding on a variety of levels. In other words, the reporting rate for each product is subject to the limitations discussed above. As a result, a comparison of two or more reporting rates also has limited reliability. Therefore, such comparisons would generally be considered exploratory or hypothesis generating. Reporting rates can by no means be considered incidence rates either for absolute or comparative purposes.

To provide context for incidence or reporting rates, it is helpful to have an estimate of the background rate for the event being evaluated in the general population or ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g., premenopausal women, diabetics). Comparisons of incidence or reporting rates to background rate estimates would ideally take into account potential differences in the data sources used to derive the incidence or reporting rates compared to those used to derive the background rate. While the extent of under-reporting is unknown, it is usually expected to be substantial. As a result, a high reporting rate may, in some cases, be a strong indicator that the true incidence rate is sufficiently high to be of concern.

B. Understanding the safety signal: who is at risk and when?

FDA has found several types of analyses useful in identifying populations at risk for an adverse event. Such analyses are possible in the context of pharmacoepidemiologic studies and may also be appropriate for evaluating spontaneously reported events if sufficient case numbers are available. In general, when submitting safety analyses to FDA, sponsors would need to describe data sources and their quality, analytic methods used, and assumptions made. Ideally, sufficient detail would be provided to allow replication of analyses. Commonly performed analyses would include:

1. Demographic analyses, such as age, gender, race, or other relevant subgroups
2. Analyses of changes in risk over calendar time or product life-cycle
3. Analyses for effect of exposure duration
4. Analyses examining dose effects, including labeled doses, greater than labeled doses and overdoses

[15] See footnote 2, Supra.

5. Analyses of the relationship between concomitant medications and potential product-product interactions and the risk of the event being evaluated
6. Analyses of the relationship between co-morbid conditions such as underlying hepatic or renal impairment and the risk of the event being evaluated
7. Analyses of the effects of lot-to-lot variation and differences in product formulation (e.g., oral vs. parenteral) and the risk of the event being evaluated
8. Analyses of the potential for an excess of adverse events given the disease being treated, such as might be observed in advanced cancer or immunocompromised patients
9. Estimates of differences from known background rates

C. Assessing causality: what factors would be considered?

For any individual case report, FDA has found that it is rarely possible to know with absolute certainty whether the event was product induced. However, a number of features, when present in a case report, are generally recognized as supportive of an association between use of a product and an adverse event. These features include the following:

1. Event occurred in the expected timeframe for that event (e.g., type 1 allergic reactions occurring within days, cancers developing after years of therapy)
2. Absence of symptoms related to the event prior to exposure
3. Absence of co-morbid conditions or use of concomitant medications that could contribute to the event
4. Availability of positive dechallenge cases in which a patient recovers after the product was discontinued
5. Availability of positive rechallenge cases in which a patient re-experiences the event after the product was re-introduced
6. Event is consistent with the established mechanism of action of the product

Consideration of these features permits cases to be grouped into categories of "probable," "possible," and "unlikely" based on the likelihood that the product was related to the adverse event.

FDA has found that it may be possible to assess the degree of causality between use of a product and an adverse event when the sponsor gathers and evaluates together all available safety data including the following:

1. Spontaneously reported and published case reports
2. Relative risks or odds ratios derived from pharmacoepidemiologic studies
3. Biologic effects observed in preclinical studies, pharmacokinetic or pharmacodynamic effects
4. Confirmatory safety findings from controlled clinical trials
5. General marketing experience with other similar products in the class

If the safety signal relates to a medication error, FDA would expect the sponsor to evaluate each event to identify the root causal factors that led to the event or possible

event. There are a number of references available describing root cause analysis.[16,17] Follow-up with reporters would be essential. A comprehensive root cause analysis would include the following characteristics:

1. Identification of failure points that led to the medication error by reviewing the medication use system (e.g., prescribing/order process, dispensing process, and administration process)
2. Looking beneath the visible cause to get at the root of the event by asking "why" questions (focusing on the systems and not on individuals)
3. Identification of prevention strategies[12]

Ideally, the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy for classifying and tracking errors would be used.[18]

D. How would safety signals be reported to FDA?

When safety signals are identified, FDA would expect sponsors to (1) submit a synthesis of all available safety information, ranging from the preclinical findings to the current observations, (2) provide an assessment of the risk/benefit profile of the product in light of this information, (3) propose steps to further investigate through additional studies and (4) propose risk management strategies as appropriate. Please refer to the concept paper *Risk Management Programs* for a discussion of possible risk management strategies.

FDA will, in turn, make its own assessment of the available data taking into account the following:

1. Magnitude of the signal
2. Precision of the risk estimates
3. Consistency of findings across available data sources
4. Biologic plausibility
5. Seriousness of the event relative to the disease being treated
6. Degree of benefit the product provides
7. Availability of other therapies
8. Potential to mitigate the safety signal in the population through various risk management strategies

VI. HOW CAN SAFETY SIGNALS BE MONITORED THROUGH ENHANCED PHARMACOVIGILANCE EFFORTS?

[16] Cohen MR (ed), 1999, *Medication Errors*, American Pharmaceutical Association, Washington DC.

[17] Cousins DD (ed), 1998, *Medication Use: A Systems Approach to Reducing Errors*, Joint Commission on Accreditation of Healthcare Organizations, Oakbrook Terrace, IL.

[18] See footnote 4, Supra.

Safety signals may become evident prior to a product's marketing approval or after a product is marketed. Plans for pharmacovigilance will depend on several factors (scientific and logistical) including the following:

1. Nature of the signal
2. Whether it occurs commonly or rarely
3. Nature of the population(s) at risk
4. Whether the product is prescribed to a broad range of patients or in selected populations only
5. Whether the product is dispensed at all pharmacies or via restricted distribution systems only

Based on experience, FDA has found that development of pharmacovigilance plans is useful at the time of product launch or when a safety signal is identified.[19]

For a product (1) without safety signals identified pre- or post-approval and (2) for which at risk populations are thought to have been adequately studied, the pharmacovigilance plan at the time of launch may simply propose that routine spontaneous reporting is sufficient for postmarketing surveillance.

For products (1) with safety signals identified pre- or post-approval, or (2) for which at-risk populations have not been adequately studied, FDA may determine that additional safety information would help to more precisely characterize the product's risk profile. If additional information is desired, FDA may request that the sponsor, either at the time of launch or when a signal is identified, develop a plan describing pharmacovigilance efforts above and beyond routine postmarketing spontaneous reporting. The proposed pharmacovigilance plan could include commitments to perform one or more of the following:

1. Submit adverse event reports in an expedited manner (i.e., as 15-day reports)
2. Submit adverse event report summaries at more frequent, pre-specified intervals (e.g., quarterly rather than annually)
3. Perform active surveillance to identify as yet unreported adverse events; such activities could focus on (a) events associated with the use of certain products, (b) events presenting for treatment at selected healthcare settings (e.g., hospitals or emergency departments), or (c) events that are often product related (e.g., acute liver failure)[20];adverse event collection mechanisms could utilize electronic health information systems and/or DHHS databases such as those maintained by the CDC, NIH or AHRQ.

[19] FDA is aware of International Conference on Harmonization (ICH) efforts to promote harmonization on the concept of pharmacovigilance plans. Consult "ICH V3: Pharmacovigilance Planning, Draft Version 1.0", discussed at Tokyo, Japan, February 2003.

[20] See footnote 6, Supra

4. Conduct additional pharmacoepidemiologic studies (in automated claims databases or other databases) using cohort, case-control or other appropriate study designs
5. Create registries or conduct patient or healthcare provider surveys
6. Conduct additional controlled clinical trials (consult the concept paper entitled, *Premarketing Risk Assessment*, for a discussion of product risk assessment in the context of controlled clinical trials)

Emerging new data may result in ongoing revisions to the sponsor's pharmacovigilance plan for a product. In some circumstances, FDA may decide to bring questions regarding safety signals, proposed pharmacovigilance plans, and findings arising from pharmacovigilance efforts before its Drug Safety and Risk Management Advisory Committee.

While additional information is being developed, FDA may decide to take interim regulatory actions to communicate information about safety signals via labeling or other means, or minimize the signal in users of the product via risk management strategies as discussed in the concept paper entitled *Risk Management Programs***.**

VII. QUESTIONS TO BE ADDRESSED AT THE PUBLIC WORKSHOP

Although FDA welcomes comment regarding all of the topics discussed in this concept paper, in particular we intend to discuss the following questions at the public workshop.

1. How can the quality of spontaneously reported case reports be improved?

2. What are possible advantages or disadvantages of applying datamining techniques (e.g., empirical Bayesian techniques, proportional reporting ratios) to spontaneous reports databases for the purpose of identifying safety signals?

3. What are possible advantages or disadvantages of performing causality assessments at the individual case level?

4. Under what circumstances would a registry be useful as a surveillance tool and when would it cease to be useful?

5. Under what circumstances would active surveillance strategies prove useful to identify as yet unreported adverse events?

6. Under what circumstances would additional pharmacoepidemiologic studies be useful?